PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION See Form PCT/IPEA/416	
PC-21017441		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE2004/001753	26-11-2004	28-11-2003
International Patent Classification (IPC) or national classification and IPC		
See Supplemental Box		
Applicant		
Mitra Medical Technology AB et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 9 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))
      _____, containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22-06-2005	20-02-2006
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Form PCT/IPEA/409 (cover sheet) (April 2005)

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Cover sheet

INTERNATIONAL PATENT CLASSIFICATION (IPC):

A61K 39/395 (2006.01)
A61K 51/10 (2006.01)
G01N 33/543 (2006.01)
C07K 17/02 (2006.01)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SE2004/001753

Box No. I Basis of the report

1. With regard to the language, this report is based on:

☐ the international application in the language in which it was filed

☐ a translation of the international application into _____ ,
which is the language of a translation furnished for the purposes of:

☐ international search (Rules 12.3(a) and 23.1(b))

☐ publication of the international application (Rule 12.4(a))

☐ international preliminary examination (Rules 55.2(a) and/or 55.3(a))

2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

☐ the international application as originally filed/furnished

☒ the description:

pages 1-44 as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☒ the claims:

pages _____ as originally filed/furnished

pages* _____ as amended (together with any statement) under Article 19

pages* 45-53 received by this Authority on 30-01-2006

pages* _____ received by this Authority on _____

☒ the drawings:

pages 1-5 as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to the sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to the sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SE2004/001753

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 33-45

because:

☒ the said international application, or the said claims Nos. 33-45 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See PCT Rule 67.1.(iv).: Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for said claims Nos. _____

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in the Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-32	YES
	Claims		NO
Inventive step (IS)	Claims	1-32	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-32	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The claimed invention relates to a conjugate comprising a trifunctional cross-linking moiety to which is coupled an affinity ligand via a linker 1, a cytotoxic agent and an anti-Erb antibody. The affinity ligand is biotin and the linker 1 is chosen so as to give stability towards enzymatic cleavage of the biotinamide bond. The linker 1 consists of ethers, thioethers, carboxylates, sulfonates or ammonium groups. The anti Erb antibody has an affinity-binding constant of at least 5x106 M-1 and in average 2-4 molecules of the three different reagents a)-c) are linked to the anti Erb antibody. The conjugate is used in pharmaceutical compositions for treating cancer expressing Erb gene products. The affinity ligand (biotin) is non-bound, which makes it possible to eliminate toxic conjugates, which have not been specifically bound to the tumour, by an extracorporeal treatment step.

Reference is made to the following documents:

D1 WO 03035011
D2 WO 0002050
D3 WO 0100244

D1 discloses a multi drug multiligand conjugate for targeted drug delivery. The conjugate is constituted of a tripartite molecule comprising a targeting molecule, a therapeutic agent and a scaffold binding element. These three parts are linked together by a core molecule, which is preferably diamino benzoic acid. Each scaffold moiety can bind up to four conjugates and during use the scaffold binding element (biotin) is bound to

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Supplemental Box

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Continuation of: Box V

the scaffold moiety.

The therapeutic agent can be a toxin or a radionuclide (see page 6, line 6) and the scaffold binding element can be biotin (see page 6, lines 29-30). The targeting molecule is any molecule that can direct the conjugate to a defined population of target cells. It can e.g. be an antibody or fragments thereof (see page 5, lines 18-25). Document D1 also discloses three examples of the following suitable targeting molecules: bombesin/gastrinreleasing peptide receptor-recognizing peptide, a somatostatin receptor recognizing peptide and an epidermal growth factor receptor recognizing peptide as well as a monoclonal antibody, or polyclonal antibody, or a receptor recognizing carbohydrate or any combination of the above.

Polyethylene glycol (PEG) is used as a linker molecule for linking the targeting molecule, the therapeutic agent and the scaffold binding moiety to the core molecule. The linker molecule reduces the effects of steric hindrance and increases the overall yield of the reaction. By using this conjugate, a more efficient delivery is achieved and therefore a lower concentration of the conjugate can be used.

D2 describes a conjugate comprising a trifunctional cross-linking moiety coupled to an affinity ligand (biotin) by linker 1, an effector agent (e.g. toxin or radionuclide), a toxin conjugate or enzyme conjugate (see page 5, lines 25-35) and a biomolecule reactive moiety. The biomolecule can be a tumor binding monoclonal antibody. The linker 1 which is to attach the biotin moiety to the trifunctional cross-linking moiety is chosen so that steric hindrances are avoided. It may also impart increased water solubility and biotinidase stabilization (see page 10, lines 19-26). The linker may

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Continuation of: Box V

contain hydrogen bonding atoms such as ethers or thioethers, or ionizable groups such as carboxylates, sulfonates, or ammonium groups, to aid in water solubilization of the biotin moiety (see page 15, lines 12-22 and claims 9-10).

This conjugate is useful for column extracorporeal immunoabsorptive removal of a radiolabeled antibody conjugate from a patient´s blood (see page 5, lines 25-35) as the affinity ligand (biotin) is non-bound.

D3 discloses a conjugate of Erb-antibodies and cytotoxic substances for targeted drug delivery for treating cancer.

The claimed invention differs from the conjugate of D1 in the linker which links biotin constitutes of ethers, thioethers, carboxylates, sulfonates or ammonium groups whereas in D1 the linker is PEG. The linker of the claimed conjugate is stable towards enzymatic degradation and the conjugate has a non-bound affinity ligand e.g. biotin. Further, the claimed conjugate is different from the conjugate in D1 in that it has several reagents coupled to the same anti Erb antibody. These differences give a stable conjugate with optimal binding to tumour surfaces and said conjugate that is not bound to tumours can be removed easier when circulating in the blood with extracorporeal elimination. In this way, an increased amount of conjugate can be administrated.

Consequently, with the background of D1, the problem is to design a conjugate comprising a suitable targeting molecule which has optimal binding to tumour surfaces so that exposure to the healthy surrounding tissue is reduced and which can be added to tumours in a higher dose.

The claimed conjugate differs from the conjugate known from D2 in that the biomolecule is an anti Erb antibody having an affinity-binding constant of at least 5x106 M-1 and wherein in average 2-4 molecules of the three different reagents a)-c) are linked to the anti Erb antibody. In D2, the biomolecule is

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preferably a tumour binding monoclonal antibody, a toxin conjugate or enzyme conjugate (see page 5, lines 27-30).

Consequently, with the background of D2, the problem is to design a conjugate comprising a multi-purpose tumour specific conjugate comprising an Erb antibody and said conjugate having optimal binding to tumour surfaces.

It is well-known to use antibodies to different known Erb-antigens and to conjugate these antibodies to different cytotoxic substances in order to lead them to cancer tumours (see D1 and D3, claims 1-3 and page 37). However, none of the documents disclose conjugates that have several reagents coupled to the same ant Erb antibody wherein the antibody has an affinity-binding constant of at least 5x106 M-1 wherein in average 2-4 molecules of the three different reagents a)-c)are linked to the anti Erb antibody.

The cited prior art does not give any indication that would lead a person skilled in the art to the claimed multi-purpose stable conjugate comprising anti Erb antibody which is easy to remove from the body when it is not bound to the tumour. It is not considered obvious to the person skilled in the art to apply these features with corresponding effect to D1 and D2 thereby arriving at a conjugate according to claim 1. The subject-matter of the claims therefore involves an inventive step.

Accordingly, the invention defined in claims 1-32 is novel and is considered to involve an inventive step. The invention is industrially applicable.

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30-01-2006

CLAIMS

1. A conjugate comprising
   a) a trifunctional cross-linking moiety, to which is coupled
   b) an affinity ligand via a linker 1 containing hydrogen bonding atoms and chosen from the group consisting of ethers, thioethers, carboxylates, sulfonates, amines, and ammonium groups,
   c) a cytotoxic agent, optionally via a linker 2, and
   d) an anti Erb antibody or variants thereof having the ability to bind to Erb antigens with an affinity-binding constant of at least $5x10^6M^{-1}$, wherein in average 2-4 molecules of the part a)-c) above are linked to the anti Erb antibody,

wherein the affinity ligand is biotin, or a biotin derivative having essentially the same binding function to avidin or streptavidin as biotin, wherein stability towards enzymatic cleavage of the biotinamide bond has been introduced in linker 1.

2. The conjugate according to claim 1, wherein the anti Erb antibody or variants thereof are directed to Erb 1, Erb 2, Erb 3, and/or Erb 4 antigens expressed on mammalian tumour surfaces.

3. The conjugate according to claim 1 or 2, wherein the anti Erb antibody variants are any modifications, fragments or derivatives of the anti Erb antibody having the same or an essentially similar affinity-binding constant of at least $5x10^6 M^{-1}$ when binding to the Erb antigen, said fragments comprising Fab, Fab′, F(ab′)2, F(ab″) and Fv fragments; diabodies; single-chain antibody molecules; and multispecific antibodies formed from anti-body fragments.

4. The conjugate according to any one of the preceding claims, wherein the anti Erb antibody is coupled to the trifunctional cross-linking moiety via a linker 3, and wherein the bond formed between linker 3 and the anti Erb antibody is either covalent or non-covalent with a binding affinity constant of at least $5x10^8\ M^{-1}$.

5. The conjugate according to any one of the preceding claims, wherein the cytotoxic agent is a radionuclide, chemotherapeutical agents, a synthetic or naturally occurring toxin, immunosuppressive or immunostimulating agents, radiosensitizers, enhancers for X-ray or MRI or ultrasound, non-radioactive elements, which can be converted to radioactive elements by means of external irradiation after the anti Erb antibody carrying said element has been accumulated to specific cells or tissues, or photoactive compounds or compounds used in photo imaging or photodynamic therapy, or any other molecule having the same or a similar effect, directly or indirectly, on cancer cells or cancer tissues.

6. The conjugate according to any one of the preceding claims, wherein the cytotoxic agent is a radionuclide, a chemotherapeutical agent, or a toxin.

7. The conjugate according to claim 6, wherein when the cytotoxic agent is a radionuclide it is bound to the trifunctional cross-linking moiety via a cytotoxic agent binding moiety.

8. The conjugate according to claim 7, wherein the cytotoxic agent binding moiety form aryl halides and vinyl halides for radionuclides of halogens, and comprises N_2S_2 and N_3S chelates for Tc and Re radionuclides, amino-carboxy derivatives, preferably EDTA, triethylenetetraaminehexaacetic acid, and DTPA or derivatives thereof, wherein the DTPA derivatives are Me-DTPA, CITC-DTPA, and cyclohexyl-DTPA, and cyclic amines, preferably NOTA, DOTA and TETA, and derivatives thereof, for In, Y, Pb, Bi, Cu, Sm and Lu radionuclides, or any other radionuclide capable of forming a complex with said chelates.

9. The conjugate according to claims 7 and 8, wherein the cytotoxic agent binding moiety comprises DOTA and the cytotoxic agent is ^{90}Y for therapeutic application or ^{111}In for diagnostic application.

10. The conjugate according to claims 6 and 7, wherein the cytotoxic agent binding moiety comprises DOTA and the cytotoxic agent is ^{177}Lu for both diagnostic and therapeutic application.

11. The conjugate according to claim 10, wherein the radionuclide is a beta radiation emitter, preferably scandium-46, scandium-47, scandium-48, copper-67, gallium-72, gallium-73, yttrium-90, ruthenium-97, palladium-100, rhodium-101, palladium-109, samarium-153, lutetium-177, rhenium-186, rhenium-188, rhenium-189, gold-198, and radium-212; a gamma emitter, preferably ioidine-131, lutetium-177 and indium-m 114; or alpha radiation emitting materials, preferably bismuth-212, bismuth-213 and astatine-211; as well as positron emitters, preferably gallium-68 and zirconium-89, wherein the chemotherapeutical agent is Adriamycin, Doxorubicin, 5-Fluorouracil, Cytosine arabinoside ("Ara-C"), Cyclophosphamide, Thioptepa, Busulfan, Cytoxin, Taxol, Methotrexate, Cisplatin, Melphalan, Vinblastine, Bleomycin, Etoposide, Ifosfamide, Mitomycin C, Mitoxantrone, Vincristine, Vinorelbine, Carboplatin, Tenisposide, Duanomysin, Carminomycin, Aminopterin, Dactinomycin, Mitomycins, Esperamicins, Maytansinoid, Melphalan and other related nitrogen mustards; and wherein the toxin is an active toxin of bacterial, fungal, plant or animal origin, or fragments thereof.

12. The conjugate according to any one of the preceding claims, wherein the affinity ligand is a moiety which binds specifically to avidin, streptavidin or any other derivatives, mutants or fragments of avidin or streptavidin having essentially the same binding function to this affinity ligand.

13. The conjugate according to any one of the

preceding claims, wherein the biotin derivative is chosen from the group consisting of norbiotin, homobiotin, oxybiotin, iminobiotin, destibiotin, diaminobiotin, biotin sulfoxide, and biotin sulfone, or derivatives thereof having essentially the same binding function, preferably with an affinity-binding constant of at least 10^9 M^{-1}.

14. The conjugate according to any one of the preceding claims, wherein the trifunctional cross-linking moiety is chosen from the group consisting of triaminobenzene, tricarboxybenzene, dicarboxyanyline and diaminobenzoic acid.

15. The conjugate according to any one of the preceding claims, wherein linker 1 serves as an attaching moiety and a spacer between the trifunctional cross-linking moiety and the affinity ligand, preferably a biotin moiety, such that binding with avidin or streptavidin, or any other biotin binding species, is not diminished by steric hindrance.

16. The conjugate according to any one of the preceding claims, wherein the stability towards enzymatic cleavage, preferably against cleavage by biotinidase, of the biotin amide bond to release biotin has been provided by introducing a methyl group on the biotinamide amine or an alpha carboxylate, a hydroxymethyl, or a methyl group or ethyl group on an atom adjacent, preferably less than three carbon atoms apart, to the biotinamide amine.

17. The conjugate according to claim 16, wherein in the case of a hydroxymethyl group the stability has been attained by the introduction of a serinyl group, and wherein in the case of a carboxyl group the stability has been attained by the introduction of an α or β aspartyl group.

18. The conjugate according to any one of the preceding claims, wherein linker 2 provides a spacer length of 1-25 atoms, preferably a length of 6-18 atoms.

19. The conjugate according to claim 18, wherein

linker 2 contains hydrogen bonding atoms, preferably ethers or thioethers, or ionisable groups, to aid in water solubilisation.

20. The conjugate according to any one of claims 1-17, wherein linker 2 is excluded.

21. The conjugate according to any one of the preceding claims, wherein linker 3 provides a spacer of a length of 1-25 atoms, preferably a length of 6-18 atoms, or groups of atoms.

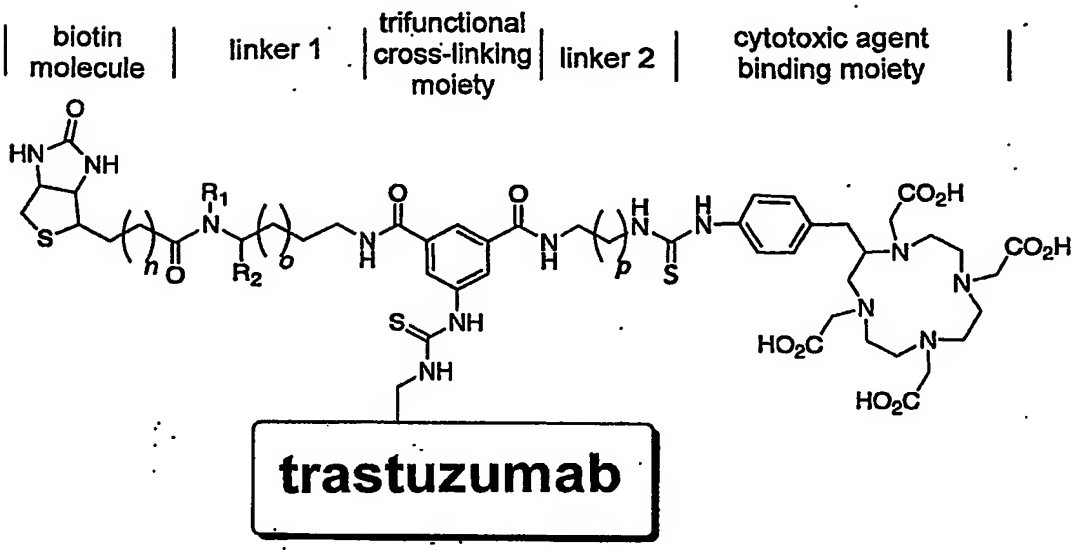
22. The conjugate according to claim 21, wherein linker 3 contains hydrogen bonding atoms such as ethers or thioethers, or ionisable groups, preferably carboxylates, sulfonates, or ammonium groups, to aid in water solubilisation.

23. The conjugate according to any one of claims 1-3 and 5-20, wherein linker 3 is excluded.

24. The conjugate according to any one of the preceding claims, wherein more than one affinity ligand, preferably two, and/or more than one cytotoxic agent, preferably two, also are bound.

25. The conjugate according to any one of the preceding claims, wherein in average 2.5-3.5 molecules of the part a)-c) of the conjugate are linked to each anti Erb antibody.

26. The conjugate according to any one of the preceding claims, wherein it is



wherein n is 2-4 , o is 1-6, p is 1-6, R_1 is H, and R_2 is -COOH, and wherein n preferably is 3, o preferably is 3, and p preferably is 3, bound to a cytotoxic agent via the cytotoxic agent binding moiety.

27. The conjugate according to any one of claims 1-25, wherein it is ^{177}Lu-1033-trastuzumab, i.e. ^{177}Lu-3-(13'-thioureabenzyl-DOTA)trioxadiamine-1-(13"-biotin-Asp-OH)trioxadiamine-5-isothiocyanato-aminoisophtalate-trastuzumab; ^{90}Y-1033-trastuzumab; ^{111}In-1033-trastuzumab; 1033-trastuzumab, wherein thioureabenzyl-DOTA has been replaced with maytansinoid; and 1033-trastuzumab, wherein thioureabenzyl-DOTA has been replaced with doxorubicin, wherein it preferably is trastuzumab with in average 2.2 MitraTag™-1033 molecules bound thereto.

28. A medical composition, wherein it comprises the conjugate according to any one of claims 1-27 together with a pharmaceutically acceptable excipient.

29. The medical composition according to claim 28, wherein the excipient is a solution intended for parenteral administration, preferably intravenous administration.

30. A kit for extracorporeal removal of or at least reduction of the concentration of a non-tissue bound medical composition as defined in any one of claims 28

and 29, comprising a conjugate according to any one of claims 1-26, in the plasma or whole blood of a mammalian host, wherein said medical composition has previously been introduced in the body of said mammalian host and kept therein a certain time in order to be concentrated to the specific tissues or cells by being attached thereto, said kit comprising

a) said medical composition, and

b) an extracorporeal device comprising an immobilized receptor onto which the affinity ligand of the conjugate adheres.

31. The kit according to claim 30, wherein it comprises antibodies and antigens/haptens or protein and cofactors as affinity ligand/immobilized receptor combinations, preferably biotin or biotin derivatives as affinity ligands and avidin or streptavidin as the immobilized receptor.

32. The kit according to claim 30, wherein the affinity ligand is absent in the conjugate of the medical composition, and the immobilized receptor is molecularily imprinted polymers interacting with the conjugate.

33. A method for the treatment of cancer expressing Erb gene products on the surface of its tumour cells in a mammalian host, wherein a medical composition according to any one of claims 28 and 29 is administered to the mammal in need thereof.

34. The method according to claim 33, wherein said cancer is breast or ovarian cancer.

35. The method according to claims 33 and 34, wherein said cancer is breast cancer, preferably of Erb 2 type.

36. The method accoding to any one of claims 33-35, wherein a medical composition according to claims 28 and 29 containing ^{90}Y as the cytotoxic agent in a dose of 10-20 MBq/kg body weight, preferably 11-15 MBq/kg body weight, is administered to the mammalian host.

37. The method according to any one of claims 33-35, wherein a medical composition according to claims 28 and 29 containing ^{90}Y as the cytotoxic agent in a dose of more than 20 MBq/kg body weight is administered to the mammalian host together with means to reconstitute the bone marrow or by reduction of the radiation effect on the bone marrow.

38. A method for diagnosing cancer expressing Erb gene products on the surface of its tumour cells in a mammalian host, wherein a medical composition according to any one of claims 28 and 29 is administered to the mammalian host.

39. The method according to claim 38, wherein said cancer is breast or ovarian cancer.

40. The method according to claims 38 and 39, wherein said cancer is breast cancer, preferably of Erb 2 type.

41. The method according to any one of claims 38-40, wherein ^{111}In in a dose of 50-200 MBq/m^2 body surface, preferably 100-150 MBq/m^2 body surface, is administered to the mammalian host.

42. A method for treatment and diagnosing of cancer expressing Erb gene products on the surface of its tumour cells in a mammalian host, wherein a medical composition acording to claims 28 and 29 containing ^{111}In in a dose of 50-200 MBq/m^2 body surface, preferably 100-150 MBq/m^2 body surface, and a medical composition according to claims 28 and 29 containing ^{90}Y as a cytotoxic agent in a dose of 10-20 MBq/kg body weight, preferably 11-15 MBq/kg body weight, are administered to the mammalian host.

43. A method for treatment and diagnosing of cancer expressing Erb gene products on the surface of its tumour cells in a mammalian host, wherein a medical composition according to claims 28 and 29 containing ^{111}In in a dose of 100-150 MBq/m^2 body surface, and a medical composition according to claims 28 and 29 containing ^{90}Y as the cytotoxic agent in a dose of more than >20 MBq/kg body

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weight, are administered to the mammalian host, either in sequence in said order by a time interval of 6-8 days or simultaneously.

44. A method for treatment and diagnosing of cancer expressing Erb gene products on the surface of its tumour cells in a mammalian host, wherein a medical composition according to claims 28 and 29 containing ^{177}Lu as the cytotoxic agent in a single dose of 555-2220 MBq/m^2 body surface, preferably 1000-2000 MBq/m^2 body surface, is administered to the mammalian host.

45. A method for treatment and diagnosing of cancer expressing Erb gene products on the surface of its tumour cells in a mammalian host, wherein a medical composition according to claims 28 and 29 containing ^{177}Lu as the cytotoxic agent in a single dose of more than 2220 MBq/m^2 body surface is administered to the mammalian host together with means to reconstitute the bone marrow or by reduction of the radiation effect on the bone marrow.